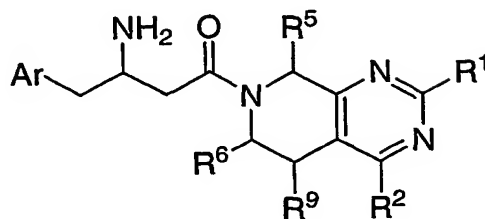


WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

Ar is phenyl which is unsubstituted or substituted with 1-5 of R³, wherein R³ is independently selected from the group consisting of:

- (1) halogen,
- (2) C₁₋₆alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (3) OC₁₋₆alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (4) CN; and
- (5) OH;

R¹ and R² are independently selected from the group consisting of:

- (1) hydrogen,
- (2) CN,
- (3) C₁₋₁₀alkyl, which is linear or branched and which is unsubstituted or substituted with:
 - (a) halogen, or
 - (b) phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴, N(C₁₋₆alkyl)SO₂R⁴, SO₂R⁴, SO₂NR⁷R⁸, NR⁷R⁸, CONR⁷R⁸, CO₂H, and CO₂C₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched,
- (4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴,

$N(C_{1-6}alkyl)SO_2R^4$, SO_2R^4 , $SO_2NR^7R^8$, NR^7R^8 , $CONR^7R^8$, CO_2H , and $CO_2C_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ is linear or branched,

- 5 (5) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, halogen, NO_2 , CN, OH, R^4 , OR^4 , $NHSO_2R^4$, $N(C_{1-6}alkyl)SO_2R^4$, SO_2R^4 , $SO_2NR^7R^8$, NR^7R^8 , $CONR^7R^8$, CO_2H , and $CO_2C_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ is linear or branched,
- 10 (6) $C_{3-6}cycloalkyl$, which is optionally substituted with 1-5 substituents independently selected from halogen, OH, $C_{1-6}alkyl$, and $OC_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ and $OC_{1-6}alkyl$ are linear or branched and optionally substituted with 1-5 halogens,
- 15 (7) OH,
- (8) OR^4 , and
- (9) NR^7R^8 ;

20 R^4 is $C_{1-6}alkyl$, which is linear or branched and which is unsubstituted or substituted with 1-5 groups independently selected from halogen, CO_2H , and $CO_2C_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ is linear or branched;

R^5 , R^6 and R^9 are independently selected from the group consisting of:

- 25 (1) hydrogen,
- (2) $C_{1-10}alkyl$, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:
- (a) halogen,
- (b) hydroxy,
- 30 (c) phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, OH, $C_{1-6}alkyl$, and $OC_{1-6}alkyl$, wherein the $C_{1-6}alkyl$ is linear or branched and optionally substituted with 1-5 halogens,
- (d) naphthyl, wherein the naphthyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, $C_{1-6}alkyl$,

- 6alkyl, and OC₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens,
- (e) CO₂H,
- (f) CO₂C₁₋₆alkyl,
- 5 (g) CONR⁷R⁸,
- (3) CN,
- (4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁₋₆alkyl, OC₁₋₆alkyl, hydroxy and halogen, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens,
- 10 (5) naphthyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁₋₆alkyl, OC₁₋₆alkyl, hydroxy and halogen, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens,
- 15 (6) CO₂H,
- (7) CO₂C₁₋₆alkyl,
- (8) CONR⁷R⁸, and
- (9) C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆alkyl, and OC₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens;
- 20

R⁷ and R⁸ are independently selected from the group consisting of:

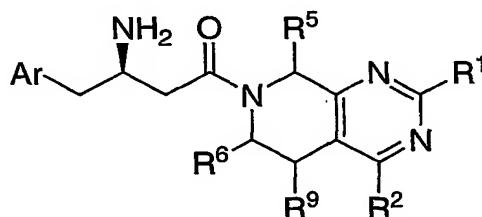
- (1) hydrogen,
- 25 (2) phenyl, which is unsubstituted or substituted with substituents independently selected from halogen, OH, C₁₋₆alkyl, and OC₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens,
- (3) C₃₋₆cycloalkyl, which is unsubstituted or substituted with substituents independently selected from halogen, OH, C₁₋₆alkyl, and OC₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens, and
- 30 (4) C₁₋₆alkyl, which is linear or branched and which is unsubstituted or substituted with:

- (a) halogen, or
 (b) phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆alkyl, and OC₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched and optionally substituted with 1-5 halogens,

or wherein R⁷ and R⁸ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof.

2. The compound of Claim 1 of the formula Ia:

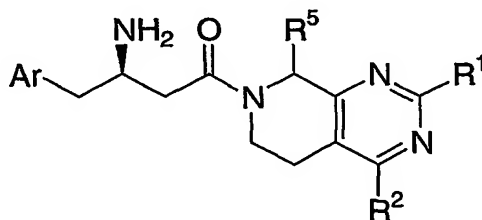


Ia

wherein Ar, R¹, R², R⁵, R⁶ and R⁹ are defined in Claim 1;

or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof.

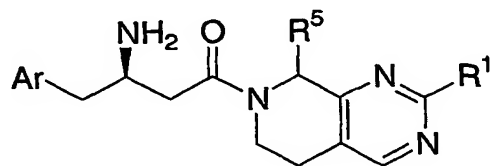
3. The compound of Claim 1 of the formula Ib:



Ib

wherein Ar, R¹, R² and R⁵ are defined in Claim 1;
or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof.

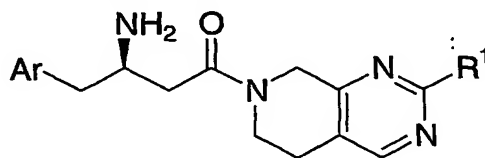
4. The compound of Claim 1 of the formula Ic:



Ic

wherein Ar, R¹ and R⁵ are defined in Claim 1;
or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof..

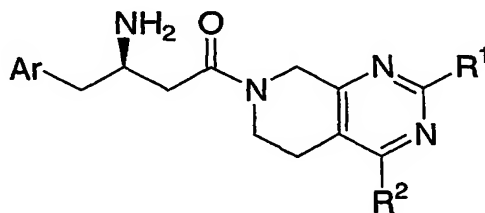
5. The compound of Claim 1 of the formula Id:



Id

wherein Ar and R¹ are defined in Claim 1;
or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof..

6. The compound of Claim 1 of the formula Ie:



Ie

wherein Ar, R¹ and R² are defined in Claim 1;
or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof..

7. The compound of Claim 1 wherein Ar is phenyl which is unsubstituted or substituted with 1-5 of R³ which are independently selected from the group consisting of:

- 5
- (1) fluoro,
 - (2) chloro,
 - (3) bromo,
 - (4) methyl,
 - (5) CF₃, and
 - (6) OH.

10

8. The compound of Claim 1 wherein Ar is selected from the group consisting of:

- 15
- (1) phenyl,
 - (2) 2-fluorophenyl,
 - (3) 3,4-difluorophenyl,
 - (4) 2,5-difluorophenyl, and
 - (5) 2,4,5-trifluorophenyl.

9. The compound of Claim 1 wherein R¹ is selected from the group consisting of:

- 20
- (1) hydrogen,
 - (2) C₁₋₆alkyl, which is linear or branched and which is unsubstituted or substituted with phenyl or 1-5 fluoro,
 - (3) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴, N(C₁₋₆alkyl)SO₂R⁴, SO₂R⁴, SO₂NR⁷R⁸, NR⁷R⁸, CONR⁷R⁸, CO₂H, and CO₂C₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched,
 - (4) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, halogen, NO₂, CN, OH, R⁴, OR⁴, NHSO₂R⁴, N(C₁₋₆alkyl)SO₂R⁴, SO₂R⁴, SO₂NR⁷R⁸, NR⁷R⁸,
- 25
- 30

CONR⁷R⁸, CO₂H, and CO₂C₁₋₆alkyl, wherein the C₁₋₆alkyl is linear or branched,

- (5) C₃₋₆cycloalkyl, and
- (6) NR⁷R⁸.

5

10. The compound of Claim 1 wherein R¹ is selected from the group consisting of:

- (1) hydrogen,
- (2) CF₃,
- 10 (3) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, methyl, CF₃, OCF₃, NHSO₂Me, NHSO₂CF₃, SO₂Me, SO₂CF₃, SO₂NH₂, NH₂, NHMe, NMe₂, and CONH₂,
- 15 (4) pyridine, pyrazine, and imidazole which is unsubstituted or substituted with 1-5 substituents independently selected from CF₃, Me, and NO₂,
- (5) cyclopropyl,
- (6) morpholine,
- (7) NH₂,
- (8) NHMe,
- 20 (9) NMe₂, and
- (10) NHCH₂Ph.

11. The compound of Claim 1 wherein R¹ is selected from the group consisting of:

- 25 (1) hydrogen,
- (2) CF₃,
- (3) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, methyl, CF₃, OCF₃, NHSO₂Me, SO₂Me, SO₂CF₃, SO₂NH₂, and CONH₂,
- 30 (4) pyridine, pyrazine, or imidazole which is unsubstituted or substituted with 1-5 substituents independently selected from CF₃, Me, and NO₂, and
- (5) cyclopropyl.

12. The compound of Claim 1 wherein R¹ is hydrogen or CF₃.

13. The compound of Claim 1 wherein R² is selected from the group consisting of:

- 5 (1) hydrogen,
- (2) C₁₋₆alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 fluoro,
- (3) OH,
- (4) OR⁴, and
- 10 (5) NR⁷R⁸.

14. The compound of Claim 1 wherein R² is selected from the group consisting of:

- (1) hydrogen,
- 15 (2) OH,
- (3) methoxy,
- (4) isopropoxy,
- (5) CF₃,
- (6) NH₂, and
- 20 (7) NHMe.

15. The compound of Claim 1 wherein R² is hydrogen.

16. The compound of Claim 1 wherein R⁵, R⁶ and R⁹ are independently selected from the group consisting of:

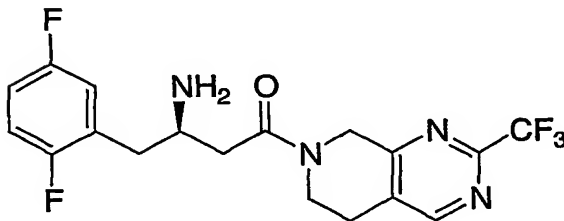
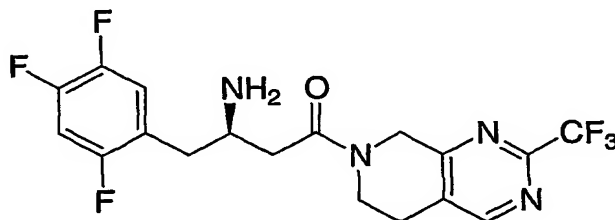
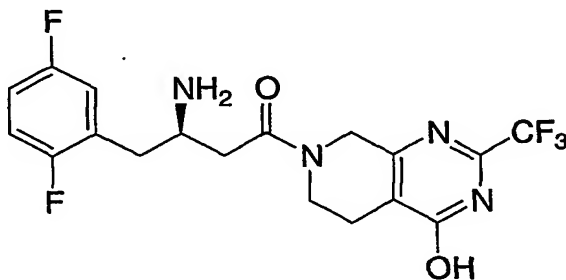
- (1) hydrogen, and
- (2) C₁₋₁₀alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:
 - (a) halogen, and
 - 30 (b) phenyl, wherein the phenyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆alkyl, and OC₁₋₆alkyl, wherein the C₁₋₆alkyl and OC₁₋₆alkyl are linear or branched and optionally substituted with 1-5 halogens.

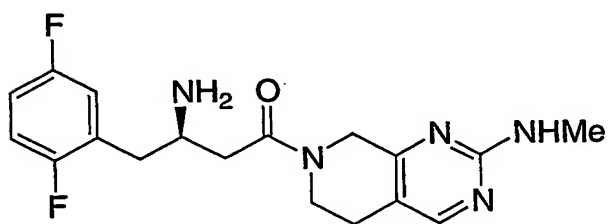
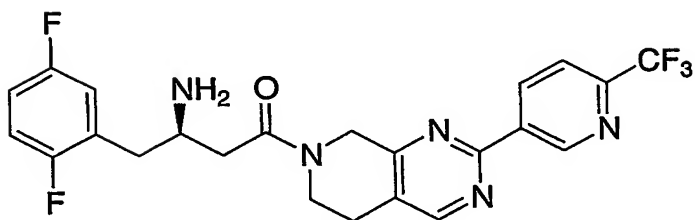
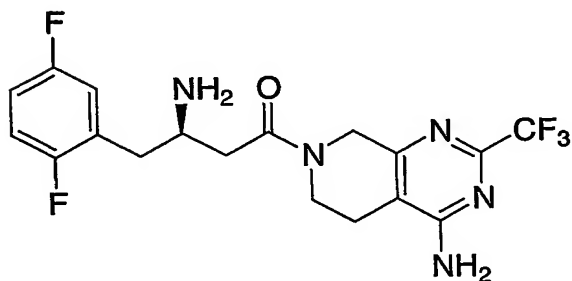
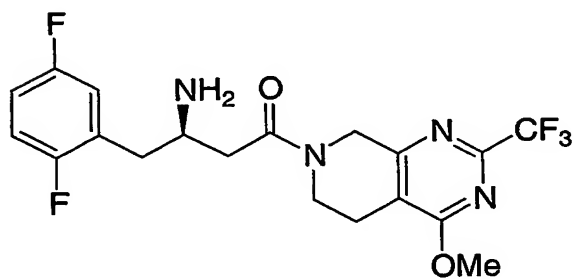
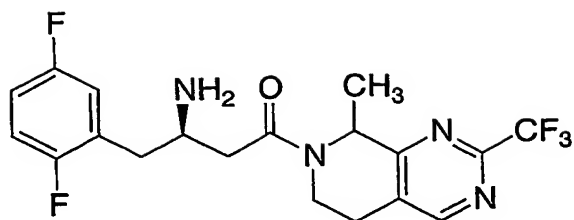
17. The compound of Claim 1 wherein R⁵, R⁶ and R⁹ are independently selected from the group consisting of:

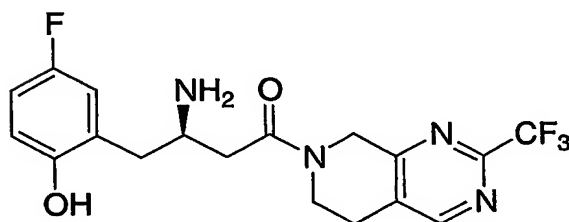
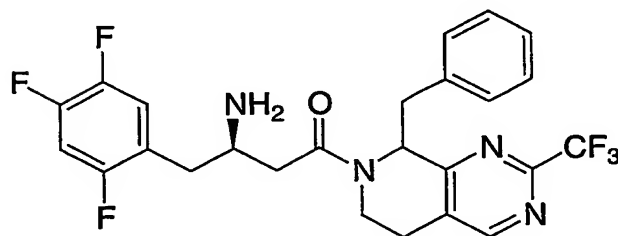
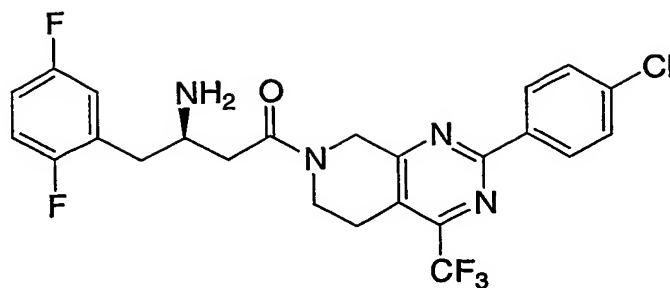
- 5 (1) hydrogen,
(2) CH₃, and
(3) CH₂-phenyl.

18. The compound of Claim 1 wherein R⁵ is H or CH₃ and R⁶ and R⁹ are hydrogen.
10

19. A compound which is selected from the group consisting of:







or a pharmaceutically acceptable salt thereof.

5

20. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

21. A method for treating, controlling, ameliorating or reducing the
10 risk of diabetes comprising the administration to a patient of an effective amount of the compound of Claim 1.

22. A method for treating, controlling, ameliorating or reducing the
risk of non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in
15 need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

23. A method for treating, controlling, ameliorating or reducing the risk of hyperglycemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

5

24. A method for treating, controlling, ameliorating or reducing the risk of obesity in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

10

25. A method for treating, controlling, ameliorating or reducing the risk of insulin resistance in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

15

26. A method for treating, controlling, ameliorating or reducing the risk of one or more lipid disorders selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

20

27. A method for treating, controlling or preventing atherosclerosis in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

25

28. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25)

35

hypertension, and other disorders where insulin resistance is a component, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

- 5 29. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type 2 diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be affected by inhibition of DP-IV, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a first compound of Claim 1, or a pharmaceutically acceptable salt thereof, and one or more other compounds selected from the group consisting of:
- (a) other dipeptidyl peptidase IV (DP-IV) inhibitors,
 - (b) insulin sensitizers selected from the group consisting of (i) PPAR γ agonists, other PPAR ligands, PPAR α/γ dual agonists, and PPAR α agonists,
 - 25 (ii) biguanides, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
 - (c) insulin or insulin mimetics;
 - (d) sulfonylureas or other insulin secretagogues;
 - (e) α -glucosidase inhibitors;
 - (f) glucagon receptor agonists;
 - 30 (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;
 - (h) GIP, GIP mimetics, and GIP receptor agonists;
 - (i) PACAP, PACAP mimetics, and PACAP receptor agonists;
 - (j) cholesterol lowering agents selected from the group consisting of
 - (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists, (v) PPAR α/γ dual agonists, (vi) inhibitors
 - 35

of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;

(k) PPAR δ agonists;

(l) antiobesity compounds;

5 (m) ileal bile acid transporter inhibitors;

(n) antihypertensives; and

(o) anti-inflammatory agents.

10 30. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which method comprises administering to a mammalian patient in need thereof a therapeutically effective amount of a compound of Claim 1 and an HMG-CoA reductase inhibitor.

15

31. The method of Claim 30 wherein the HMG-CoA reductase inhibitor is a statin.

20 32. The method of Claim 31 wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

25 33. A method for treating, controlling, ameliorating or reducing the risk of atherosclerosis in a mammalian patient in need thereof comprising the administration to the patient of an effective amount of a compound of Claim 1 and an effective amount of an HMG-CoA reductase inhibitor.

30 34. The method as recited in Claim 33 wherein the HMG-CoA reductase inhibitor is a statin.

30

35. The method as recited in Claim 34 wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

36. A pharmaceutical composition for treating, controlling, ameliorating or reducing the risk of atherosclerosis, comprising: (1) a compound of Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

5

37. A pharmaceutical composition comprising
(1) a compound of Claim 1,

(2) one or more compounds selected from the group consisting of :

- 10 (a) other dipeptidyl peptidase IV (DP-IV) inhibitors;
(b) insulin sensitizers selected from the group consisting of (i) PPAR γ agonists, other PPAR ligands, PPAR α/γ dual agonists, and PPAR α agonists, (ii) biguanides, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
(b) insulin or insulin mimetics;
(c) sulfonylureas or other insulin secretagogues;
15 (d) α -glucosidase inhibitors;
(f) glucagon receptor agonists;
(g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;
(h) GIP, GIP mimetics, and GIP receptor agonists;
(i) PACAP, PACAP mimetics, and PACAP receptor agonists;
20 (j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotiny alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists, (v) PPAR α/γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;
25 (k) PPAR δ agonists;
(l) antiobesity compounds;
(m) ileal bile acid transporter inhibitors;
(n) antihypertensives; and
(o) anti-inflammatory agents; and
30 (3) a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of Claim 37 wherein the PPAR α/γ dual agonist is KRP-297.

39. A method of treating diabetes in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with the PPAR α/γ dual agonist KRP-297.